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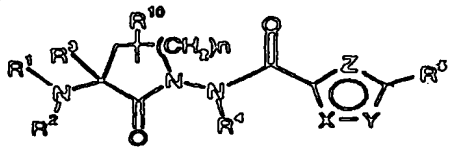
(54) Title: PROTEASE INHIBITORS

(57) Abstract

This invention relates to compounds of formula (I) wherein: X, Y and Z independently are N, O, S or CR', provided that at least two of X, Y and Z are heteroatoms and at least one of X, Y and Z is N; or one of X, Y and Z is C=N, C=C or N=N and the other two are CR' or N, provided that X, Y and Z together comprise at least two N; ⎯⎯ indicates a single or double bond; R^1 is R'', R''C(O), R''C(S), R''SO_2, R''OC(O), or R''OC(O)NR'CH(R^6)C(O); R^2 is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar–C_{0-6}alkyl, or Het–C_{0-6}alkyl; R^3 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl–C_{0-6}alkyl, Ar–C_{0-6}alkyl, or Het–C_{0-6}alkyl; R^4 is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar–C_{0-6}alkyl, or Het–C_{0-6}alkyl; R^5 is C_{1-6}alkyl, Ar–C_{0-6}alkyl, Het–C_{0-6}alkyl, CH(R^6)NR'R^7, CH(R^6)Ar, CH(R^6)OAr, or NR^8R^9; R_6, R_7, R_8 and R_9 are as defined in the description; R^{10} is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl–C_{0-6}alkyl, Ar–C_{0-6}alkyl, or Het–C_{0-6}alkyl; n is 1, 2 or 3; or a pharmaceutically acceptable salt thereof, which are inhibitors of cysteine porteases, particularly cathepsin K, and are useful in the treatment of diseases in which inhibition of bone loss is a factor.



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PROTEASE INHIBITORS

Field of the Invention

This invention relates to novel protease inhibitors, particularly inhibitors of cysteine and serine proteases, more particularly compounds which inhibit cysteine proteases, even more particularly compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly compounds which inhibit cysteine proteases of the cathepsin family, most particularly compounds which inhibit cathepsin K. Such compounds are particularly useful for treating diseases in which cysteine proteases are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis, and arthritis.

Background of the Invention

Cathepsin K is a member of the family of enzymes which are part of the papain superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Patent No. 5,501,969 (called cathepsin O therein). Cathepsin K has been recently expressed, purified, and characterized. Bossard, M. J., et al., (1996) *J. Biol. Chem.* **271**, 12517-12524; Drake, F.H., et al., (1996) *J. Biol. Chem.* **271**, 12511-12516; Bromme, D., et al., (1996) *J. Biol. Chem.* **271**, 2126-2132.

Cathepsin K has been variously denoted as cathepsin O, cathepsin X or cathepsin O2 in the literature. The designation cathepsin K is considered to be the more appropriate one (name assigned by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology).

Cathepsins of the papain superfamily of cysteine proteases function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated in various disease states, including but not limited to, infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei brucei, and Crithidia fusiculata; as well as in schistosomiasis malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and the like. *See* International Publication Number WO 94/04172, published on March 3, 1994, and references cited therein. *See also* European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine

proteases from P. gingivallis, called gingipains, have been implicated in the pathogenesis of gingivitis. Potempa, J., et al. (1994) *Perspectives in Drug Discovery and Design*, **2**, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

It now has been discovered that a novel class of compounds are protease inhibitors, most particularly inhibitors of cathepsin K, and these compounds are useful for treating

diseases in which inhibition of bone resorption is indicated, such as osteoporosis and periodontal disease.

Summary of the Invention

An object of the present invention is to provide protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly such compounds which inhibit cysteine proteases, even more particularly such compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly such compounds which inhibit cysteine proteases of the cathepsin family, most particularly such compounds which inhibit cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases.

Accordingly, in the first aspect, this invention provides a compound according to Formula I.

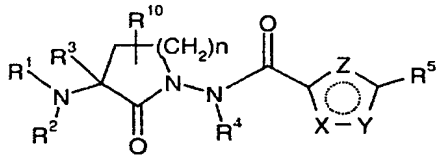
In another aspect, this invention provides a pharmaceutical composition comprising a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient.

In yet another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, most particularly cathepsin K.

In a particular aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

Detailed Description of the Invention

The present invention provides compounds of formula (I):



(I)

wherein:

X, Y and Z independently are N, O, S or CR', provided that at least two of X, Y and Z are heteroatoms and at least one of X, Y and Z is N; or one of X, Y and Z is C=N, C=C or N=N and the other two are CR' or N, provided that X, Y and Z together comprise at least two N;

--- indicates a single or double bond;

R^1 is R", R"C(O), R"C(S), R"SO_2, R"OC(O), or R"OC(O)NR'CH(R^6)C(O);

R^2 is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^3 is H, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^4 is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^5 is C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, CH(R^6)NR'R^7, CH(R^6)Ar, CH(R^6)OAr, or NR^8R^9;

each R^6 independently is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl;

R^7 is R", R"C(O), R"C(S), R"SO_2, R"OC(O), or R"OC(O)NR'CH(R^6)C(O);

R^8 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl and R^9 is C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; or R^8 and R^9 are combined to form a 3-7 membered monocyclic or 7-10-membered bicyclic carbocyclic or heterocyclic ring, optionally substituted with 1-4 of C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkoxy, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}$NR'R", or O$(CH_2)_{1-6}$NR'R";

R^{10} is H, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

each R' independently is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

each R" independently is C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; and

n is 1, 2 or 3;

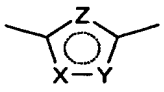
or a pharmaceutically acceptable salt thereof.

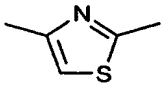
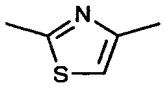
The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to formula (I) *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans

(E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in formula (I) or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

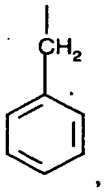
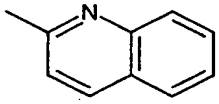
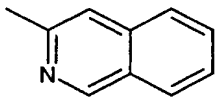
With respect to formula (I):

Suitably  is

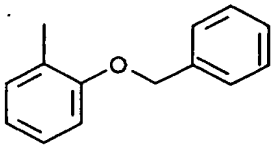
 or  .

Suitably, R^2, R^4 and R^{10} are H and R^3 is H, C_{1-6}alkyl, C_{2-6} alkenyl or C_{3-6}cycloalkyl-CH_2.

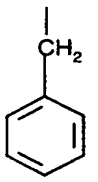
Preferably, R^5 is $CH(R^6)NR'R^7$, in which R^6 is i-butyl and R' is H. More preferably, R^7 is R"OC(O) or R"C(O), in which R" is C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl, and, most preferably, R" is

 ,  or 

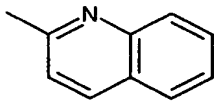
Alternately, R^5 is Ar, in which Ar in said R^5 group is



Suitably, R^1 is R"OC(O) or R"C(O), in which R" in said R^1 group is

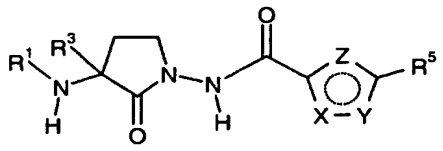


or



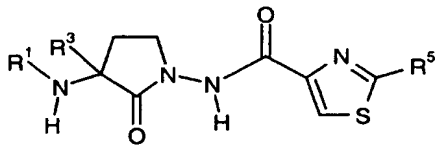
Suitably, n is 1 or 2. Preferably, n is 1.

In one particular embodiment, this invention is a compound of formula (II):



(II)

Preferably, the formula (II) compound of this invention is a compound of formula (IIa):



(IIa)

Specific representative compounds of this invention are:
1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;

1-({2-[(1S)-1-(tert-butoxycarbonylamino)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-amino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-(2-quinolinylcarboxamido)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-(3-isoquinolinylcarboxamido)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
(3S)-3-allyl-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]pyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(cyclopropylmethyl)pyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-propylpyrrolidin-2-one;
(3S)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(2-methylallyl)pyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(2-methylpropyl)pyrrolidin-2-one;
(3R)-3-(2-methylpropyl)-1-[2-(1-napthyl)phenylthiazol-4-ylcarboxamido]-3-(8-quinolinecarboxamido)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-methylpropyl)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-[2-(1-napthyl)phenylthiazol-4-ylcarboxamido]-(3R)-3-(8-quinolinecarboxamido)pyrrolidin-2-one; and
3-benzyloxycarbonylamino-1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-methylpropyl)pyrrolidin-2-one;
or pharmaceutically acceptable salts thereof.

In yet another aspect of this invention is provided novel intermediates useful in the preparation of formula (I) compounds represented by:
2-benzyloxyphenylboronic acid;
ethyl 2-(2-benzyloxyphenyl)thiazol-4-carboxylate;
2-(2-benzyloxyphenyl)thiazol-4-carboxylic acid;
(3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one;
(3S)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one;
1-(*tert*-butoxycarbonylamino)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;

1-(*tert*-butoxycarbonylamino)-(3S)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
(1S)-1-benzyloxycarbonylamino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane;
2-[(1S)-1-benzyloxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid;
(1S)-1-tert-butoxycarbonylamino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane;
2-[(1S)-1-*tert*-butoxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid;
(3S)-3-allyl-3-(benzyloxycarbonylamino)-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one;
(3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)-3-propylpyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-(*tert*-butoxycarbonylamino)-3-(cyclopropylmethyl)pyrrolidin-2-one; and
(3S)-3-(benzyloxycarbonylamino)-1-(*tert*-butoxycarbonylamino)-3-(2-methylallyl)pyrrolidin-2-one.

These intermediates are prepared using the methods described in Schemes 1-4 and the Examples described hereinafter.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). The term "amino acid" as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

"C_{1-6}alkyl" as applied herein is meant to include substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C_{1-6}alkyl group may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or C_{1-4}alkyl, where R' is H or C_{1-6}alkyl. C_0alkyl means that no alkyl group is present in the moiety. Thus, Ar-C_0alkyl is equivalent to Ar.

"C_{3-6}cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

"C_{2-6} alkenyl" as applied herein means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C_{2-6}alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

"C_{2-6}alkynyl" means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C_{2-6} alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

"Halogen" or "halo" means F, Cl, Br, and I.

"Ar" or "aryl" means unsubstituted phenyl or naphthyl; or phenyl or naphthyl substituted by one or more of Ph-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkoxy, Ph-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR'R'$, $O(CH_2)_{1-6}NR'R'$; wherein each R' independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; or phenyl or naphthyl substituted by one to three moieties selected from C_{1-4}alkyl, OR', $N(R')_2$, SR', CF_3, NO_2, CN, CO_2R', CON(R'), F, Cl, Br and I.

As used herein "Het" or "heterocyclic" represents a stable 5- to 7-membered monocyclic or a stable 7- to 10-membered bicyclic heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one or two moieties selected from C_{1-4}alkyl, OR', $N(R')_2$, SR', CF_3, NO_2, CN, CO_2R', CON(R'), F, Cl, Br and I, where R' is C_{1-6}alkyl. Examples of such heterocycles include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6-napthyridinyl, 1,7-napthyridinyl, 1,8-napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl.

"HetAr" or "heteroaryl" means any heterocyclic moiety encompassed by the above definition of Het which is aromatic in character, e.g., pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7- napthyridinyl, 1,8- napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl.

It will be appreciated that the heterocyclic ring described as 

includes thiazoles, oxazoles, triazoles, thiadiazoles, oxadiazoles, isoxazoles, isothiazols, imidazoles, pyrazines, pyridazines, pyrimidines, triazines and tetrazines which are available by routine

chemical synthesis and are stable. The single and double bonds (i.e., ---) in such heterocycles are arranged based upon the heteroatoms present so that the heterocycle is aromatic (e.g., it is a heteroaryl group). The term heteroatom as applied herein refers to oxygen, nitrogen and sulfur. When the heteroaryl group comprises a five membered ring, W is preferably an electron withdrawing group, such as halogen, -CN, $-CF_3$, $-NO_2$, $-COR'$, $-CO_2R'$, $-CONHR'$, $-SO_2NHR'$, $-NHSO_2R'$, $-NHCOR'$, -O-COR', -SR' or NR'R', or a similar electron withdrawing substituent as known in the art.

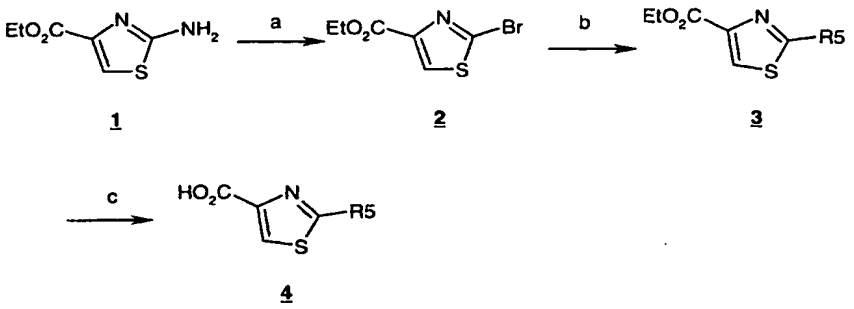
Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc or BOC refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz or CBZ refers to the benzyloxycarbonyl radical.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP is 2,6-dimethylaminopyridine, EDC or EDCI refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBT or HOBt refers to 1-hydroxybenzotriazole, DMF refers to dimethyl formamide, BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, DMAP is dimethylaminopyridine, Lawesson's reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, NMM is N-methylmorpholine, TFA refers to trifluoroacetic acid, TFAA refers to trifluoroacetic anhydride, KHMDS refers to potassium hexamethyldisilazide, and THF refers to tetrahydrofuran. Jones reagent is a solution of chromium trioxide, water, and sulfuric acid well-known in the art.

Certain intermediates useful in the preparation of formula (I) compounds are prepared by processes analogous to those described in *Justus Liebigs Ann. Chem.*, **1988**, 1127 (synthesis of diprotected (S)-1,3-diaminopyrrolidinone), *Collect. Czech. Chem. Commun.*, **1968**, *33*, 3065 (synthesis of (S)-1,3-diaminopiperidin-2-one), *Tetrahedron Lett.*, **1996**, *37*, 4319; *J. Org. Chem.*, **1985**, *50*, 3631; *ibid*, **1982**, 47, 104; Science, **1980**, *210*, 656 (synthesis of aminopyrrlodinone).

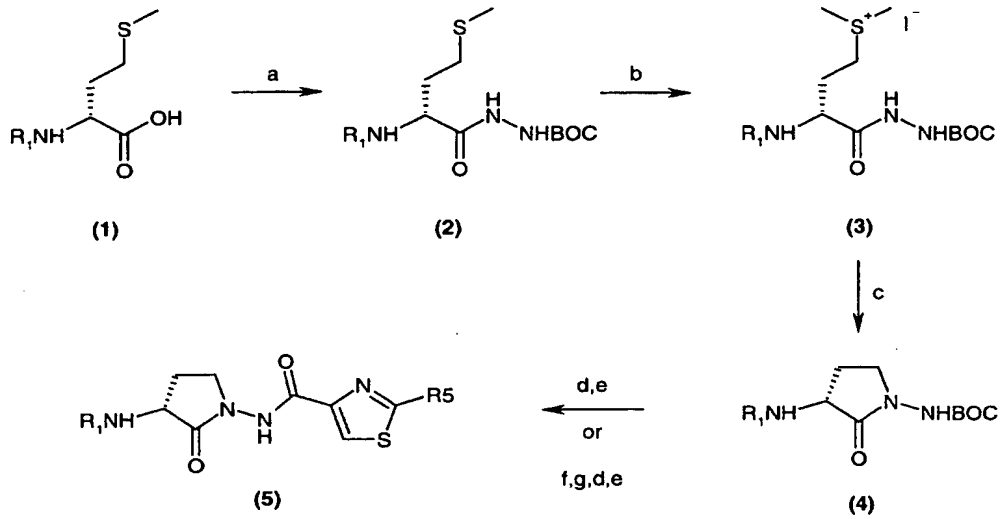
Compounds of the formula (I) wherein R^1 is alkyl or aromatic carbamate or amide, R^2, R^3 and R^4 are H, R^5 is unsubstituted or substituted aromatic, Z is N, X is CH, Y is S, and n is 1 are prepared by methods analogous to those described in Schemes 1 and 2.

Scheme 1



a) $NaNO_2$, HBr, CuBr, H_2O; b) $R^4B(OH)_2$, $Pd(PPh_3)_4$, EtOH, toluene; c) NaOH, MeOH

Scheme 2



a) NH_2NHBOC, EDCI, HOBt, DMF; b) MeI; c) NaH, DMF, CH_2Cl_2; d) HCl, 1,4-dioxane; e) thiazole-CO_2H, EDCI, HOBt, NMM, DMF; f) H_2, Pd-C, EtOH; g) R^1CO_2H, EDCI, HOBt, DMF.

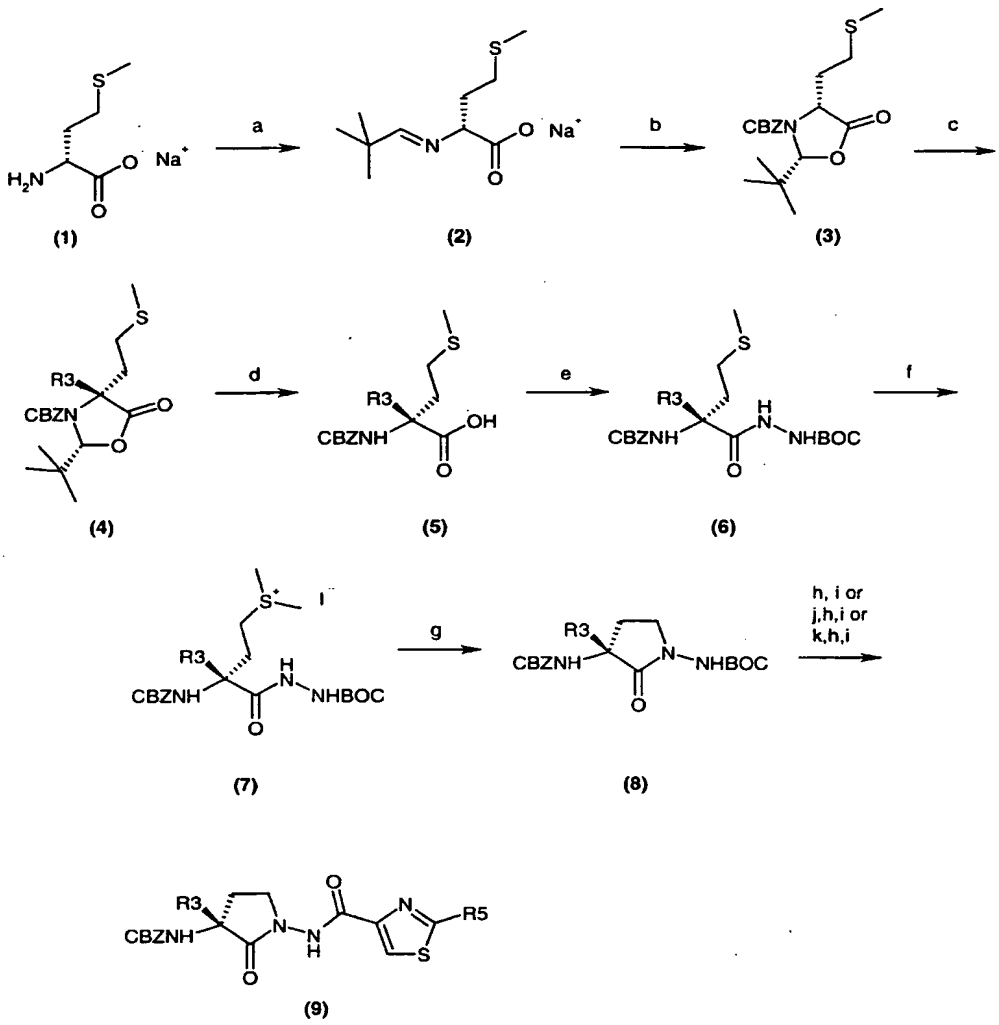
The 2-aminothiazole 1-Scheme 1 is readily prepared by the condensation of thiourea with ethyl bromopyruvate in acetone at 45°C. Diazotisation of 1-Scheme 1 is performed with sodium nitrite in aqueous acidic media, such as hydrobromic acid, and the resulting diazo compound treated with copper bromide affording the bromothiazole 2-

Scheme 1. Coupling of 2-Scheme 1 with an aryl boronic acid, such as 2-benzyloxyphenyl-boronic acid or 1-napthylboronic acid, is carried out using catalytic tetrakis(triphenyl-phosphine)palladium and a base, such as sodium hydrogen carbonate, in refluxing toluene/ethanol to afford 3-Scheme 1. Hydrolysis to the corresponding carboxylic acid 4-Scheme 1 occurs readily at room temperature on treatment with aqueous base, such as sodium hydroxide of lithium hydroxide.

D-Methionine (or L-methionine - not shown) is treated with a chloroformate, such as benzylchloroformate, in the presence of base, such as aqueous sodium hydroxide, to afford 2-Scheme 1. Condensation of 2-Scheme 1 with *tert*-butyl carbazate in the presence of a peptide coupling reagent, such as EDCI.HCl/HOBt, in an aprotic solvent, such as DMF, provides 2-Scheme 2. Treatment of 2-Scheme 2 with methyl iodide affords the corresponding sulfonium salt 3-Scheme 2, which cyclises upon treatment with a base, such as sodium hydride or potassium *tert*-butoxide, in an aprotic solvent, such as DMF, dichloromethane or THF, affording the pyrrolidinone 4-Scheme 2. Optionally, 4-Scheme 2. 4-Scheme 2 (R^1 = CBZ) is hydrogenated in the presence of catalytic palladium on charcoal and the resulting amine coupled with an appropriate carboxylic acid, such as quinoline-2-carboxylic acid or isoquinoline-3-carboxylic acid, to afford the corresponding amide 4-Scheme 2 (R^1 = RCO). Removal of the *tert*-butoxycarbonyl protecting group is carried out by treatment with an appropriate acid, such as hydrochloric acid of trifluoroacetic acid, in an aprotic solvent, such as 1,4-dioxane of dichloromethane, and the resulting amine hydrochloride is immediately coupled with an appropriate thiazole carboxylic acid (4-Scheme 1) in the presence of a peptide coupling reagent, such as EDCI.HCl/HOBt, and a base, such as N-methylmorpholine, in an aprotic solvent, such as DMF, to provide the hydrazides 5-Scheme 2.

Compounds of the formula (I) wherein R^1 is alkyl or aromatic carbamate or amide, R^2 and R^4 are H, R^3 is C_{1-6}alkyl $R^5$is unsubstituted or substituted aromatic, Z is N, X is CH, Y is S, and n is 1 are prepared by methods analogous to those described in Scheme 3.

Scheme 3



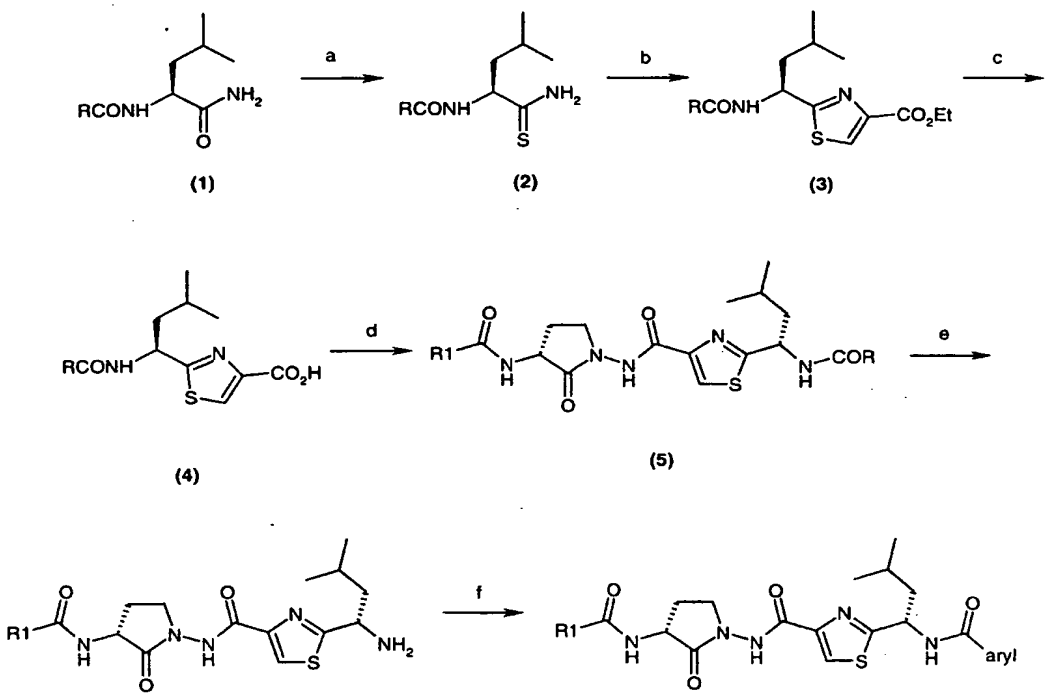
a) $(CH_3)_3CCHO$, hexanes; b) CBZCl, CH_2Cl_2; c) KHMDS, THF, R^3Br or R^3I; d) NaOH, MeOH, H_2O; e) NH_2NHBOC, EDCI, HOBt, DMF; f) MeI; g) NaH, DMF, CH_2Cl_2; h) HCl, 1,4-dioxane; i) R^5CO_2H, EDCI, HOBt, NMM, DMF; j) CH_2N_2, $Pd(OAc)_2$, Et_2O; k) H_2, Pd-C, EtOH.

D-Methionine was converted into the sodium salt 1-Scheme 3 upon treatment with sodium hydroxide in aqueous ethanol. Treatment of 1-Scheme 3 with trimethyl-acetaldehyde in an appropriate solvent, such as pentane or hexane, at reflux affords the

imine 2-Scheme 3 which is further treated with a chloroformate, such as benzyl chloroformate, at low temperature (-15 to 5°C) in an appropriate solvent, such as dichloromethane or chloroform, to give the oxazolidinone 3-Scheme 3. Treatment of 3-Scheme 3 with a base, such as potassium bis(trimethysilyl)amide, in an appropriate sovent, such as mixtures of THF and toluene, at low temperature (-78°C) followed by reaction with an electrophile, such as allyl bromide, methallyl bromide or methyl iodide, affords 4-Scheme 3. Hydrolysis of 4-Scheme 4 with an appropriate base, such as aqueous sodium hydroxide, in refluxing aqueous methanol affords 5-Scheme 3. Condensation 5-Scheme 3 with *tert*-butyl carbazate in the presence of a peptide coupling reagent, such as EDCI.HCl/HOBt, in an aprotic solvent, such as DMF, provides 6-Scheme 3. Treatment of 6-Scheme 3 with methyl iodide affords the corresponding sulfonium salt 7-Scheme 3 which cyclises upon treatment with a base, such as sodium hydride or potassium *tert*-butoxide, in an aprotic solvent, such as DMF, dichloromethane or THF, affording the pyrrolidinone 8-Scheme 3. Optionally, 8-Scheme 3 (R^3 = allyl) is treated with palladium diacetate and ethereal diazomethane at a low temperature (-5 to 5°C) to afford 8-Scheme 3 (R^3 = cyclopropylmethyl) or 8-Scheme 3 (R^3 = allyl), which is hydrogenated in the presence of catalytic palladium on charcoal to give 8-Scheme 3 (R^3 = propyl). Removal of the *tert*-butoxycarbonyl protecting group from 8-Scheme 3 is carried out by treatment with an appropriate acid, such as hydrochloric acid of trifluoroacetic acid, in an aprotic solvent, such as 1,4-dioxane of dichloromethane, and the resulting amine hydrochloride is immediately coupled with an appropriate thiazole carboxylic acid (4-Scheme 1) in the presence of a peptide coupling reagent, such as EDCI.HCl/HOBt, and a base, such as N-methylmorpholine, in an aprotic solvent, such as DMF, to provide the hydrazides 9-Scheme 3.

Compounds of the formula (I) wherein R^1 is alkyl or aromatic carbamate or amide, R^2, R^3 and R^4 are H, R^5 is arylcarboxamido or alkoxy- or aryloxycarbonylamino-substituted alkyl, Z is N, X is CH, Yis S, and n is 1 are prepared by methods analogous to those described in Scheme 4.

Scheme 4



a) Lawesson's reagent, THF; b) EtO_2CCOCH_2Br, acetone; c) LiOH, THF, H_2O; d) 1-aminopyrrolidinone, EDCI, HOBt, NMM, DMF; e) HCl, 1,4-dioxane; f) $ArylCO_2H$, EDCI, HOBt, NMM, DMF.

A commercially available urethane protected L-leucine (such as CBZ-leucine or BOC-leucine) was treated with isobutyl chloroformate in the presence of N-methyl morpholine then with methanolic ammonia to give 1-Scheme 4. Treatment of 1-Scheme 4.with Lawesson's reagent afforded the thioamide 2-Scheme 4, which was condensed with ethyl bromopyruvate in acetone at 45°C to afford 3-Scheme 4. Hydrolysis to the corresponding carboxylic acid 4-Scheme 4 occurs readily at room temperature on treatment with aqueous base, such as sodium hydroxide of lithium hydroxide. Condemsation with an appropriate 1-aminopyrrolidinone, such as 1-amino-(3R)-3-(benzyloxycarbonyl)pyrrolidin-2-one, in the presence of a peptide coupling reagent, such as EDCI.HCl/HOBt, in an aprotic solvent, such as DMF, provides 5-Scheme 4. Optionally, 5-Scheme 4, R - *tert*-butoxy) is treated with hydrochloric acid in 1,4-dioxane to afford 6-Scheme 4, which is then coupled with an appropriate carboxylic acid, such as quinoline-2-carboxylic acid or isoquinoline-3-carboxylic acid, to afford 7-Scheme 4 compounds.

The starting materials used herein are commercially available amino acids or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience). The unnatural amino acids starting materials, such as side-chained substituted methionine for formula (I) compounds wherein n is 1 and side-chained substituted ornithine for formula (I) compounds wherein n is 2, are readily prepared using standard amino acid syntheses known in the art, for example glycine alkylation and Strecker synthesis, to prepare formula (I) compounds wherein R^{10} is other than H.

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). The term "amino protecting groups" generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

Acid addition salts of the compounds of formula (I) are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as

hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds of formula (I) are useful as protease inhibitors, particularly as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis,

metachromatic leukodystrophy, muscular dystrophy, amytrophy; and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of malignancy, and metabolic bone disease.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof a compound of the present invention. The present invention especially provides methods of treatment of diseases caused by pathological levels of cathepsin K, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof an inhibitor of cathepsin K, including a compound of the present invention.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to a patient of an effective amount of a compound of formula (I), alone or in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

For acute therapy, parenteral administration of a compound of formula (I) is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Determination of cathepsin K proteolytic catalytic activity

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry*, **1989**, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\,app}) + A] \qquad (1)$$

where v is the velocity of the reaction with maximal velocity V_m , A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[AMC] = v_{ss}\, t + (v_0 - v_{ss})\,[1 - exp\,(-k_{obs}t)] / k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

Human Osteoclast Resorption Assay

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber.

Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to 1.5×10^4/mL in EMEM

medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

Examples

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1

Preparation of 1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

a) ethyl 2-aminothiazole-4-carboxylate hydrobromide

To a stirred suspension of thiourea (6.0 g, 78.8mmol) in ethanol (80mL) was added ethyl bromopyruvate (15.4 g, 78.8mmol). The resulting solution was heated at 45 °C for 23 h. The solution was cooled at 0 °C for 24 h, and the crystals were collected by filtration and washed with cold ethanol to provide the title compound (15.8 g, 79%). ^{1}H NMR (400 MHz, CD_3OD) d 7.70 (s, 1H), 4.41 (q, 2H), 1.38 (t, 3H).

b) ethyl 2-bromothiazole-4-carboxylate

To a stirring suspension of the compound of Example 1(a) (12.15 g, 48mmol) in 16% aqueous HBr (150mL), cooled to 0 °C, was added dropwise a solution of sodium nitrite (3.44 g, 49.8mmol) in water (6mL). After stirring for 35 min, copper (I) bromide (7.83 g, 54.6mmol) and 16% aqueous HBr (60mL) were added and the mixture was heated at 70 °C for 1 h. The mixture was filtered and the filtrate was saturated with NaCl then extracted with ethyl acetate (2 X 170mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was combined with combined with the solid collected in the first filtration, heated at reflux in ethanol (500mL) for 5 min, then filtered. To the filtrate was added 1.5mL of 48% aqueous HBr and the solution was heated at reflux for 16 h, then concentrated. The residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The organic layer was washed with saturated brine, dried (MgSO4), decolorized with charcoal, filtered and concentrated to provide the title compound as a pale yellow solid (7.46 g, 75%). MS (ESI): 236.0 $(M+H)^+$.

c) 2-benzyloxybromobenzene

To a stirring solution of 2-bromophenol (10.0 g, 57.8mmol), and benzyl bromide (9.9 g, 57.8mmol) in acetone (150mL) was added K_2CO_3 (12.0 g, 86.7mmol). After stirring at reflux for 4h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a colorless oil (15.2 g, 57.8mmol). ^{1}HNMR (400 MHz, $CDCl_3$) d 7.62 (m, 1H), 7.54 (m, 2H), 7.45 (m, 2H), 7.37 (m, 1H), 7.28 (m, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 5.17 (s, 2H).

d) 2-benzyloxyphenylboronic acid

To a stirring solution of the compound of Example 1(c) (15.2 g, 57.8mmol) in THF (100mL) at -78°C was added dropwise *n*-BuLi (23.1mL, 2.5M in hexane, 57.8mmol). The mixture stirred at -78°C for 25 min when added via cannulation to a stirring solution of triisopropylborate (54.4 g, 289mmol) in THF (100mL) at -78°C. After warming to room temperature and stirring for 3h, the mixture was poured into 3N HCl (100mL) and extracted with ethyl acetate (3 X 200mL). The organic layers were combined, washed successively with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a pale yellow solid (6.9 g, 30.3mmol). ^{1}HNMR (400 MHz, $CDCl_3$) d 7.90 (d, 1H), 7.42 (m, 6H), 7.07 (t, 1H), 7.02 (d, 1H), 6.05 (s, 2H), 5.16 (s, 2H).

e) ethyl 2-(2-benzyloxyphenyl)thiazole-4-carboxylate

To a stirring solution of the compound of Example 1(b) (4.0 g, 16.9mmol), the compound of Example 1(d) (4.29 g, 18.8mmol), tetrakis(triphenylphosphine)palladium(0) (0.65 g, 0.57mmol) in dimethoxyethane (60mL) was added cesium fluoride (8.58 g, 56.5mmol) and the mixture was heated at 85 °C for 16 h. Tetrakis(triphenylphosphine)palladium(0) (0.65 g, 057mmol) was added and heating at 85 °C was continued for 5 h. The mixture was diluted with water (60mL) and extracted with ethyl acetate (2 X 120mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on 180 g of 230-400 mesh silica gel, eluting with 15% ethyl acetate in hexanes, to provide the title compound as a white solid (3.22 g, 56%). MS (ESI): 340.3 $(M+H)^+$.

f) 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid

To a stirring solution of the compound of Example 1(e) (184.2 mg, 0.54mmol) in 1:1 THF/water (4mL) was added lithium hydroxide monohydrate (68.3 mg, 1.63mmol). The mixture was allowed to stir for 5 h at room temperature, then acidified with 1 N HCl and extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), filtered and concentrated to give the title compound as an off-white solid (165.5 mg, 98%). MS (ESI): 312.2 $(M-H)^-$.

g) benzyloxycarbonyl-D-methionine

A solution of D-leucine (29.8g, 0.20mol) in 10% aqueous sodium hydroxide (75.0mL, 0.21mol) was cooled to 0°C then treated alternately in ten portions with benzyl chloroformate (31.4mL; 0.22mol) and 10% aqueous sodium hydroxide (79.0mL, 0.22mol) and the solution was allowed to stir at room temperature for 1h. The mixture was then extracted with diethyl ether (2X) and the aqueous layer acidified with 6N hydrochloric acid and extracted with diethyl ether. The extracts were dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless solid (47.0g, 83%). mp 62-63°C.

h) N-[benzyloxycarbonylamino-D-methioninyl)-N'-(*tert*-butoxycarbonyl)hydrazide

A solution of the compound from example 1(g) (20.0g, 70.7mmol), *tert*-butoxycarbonylhydrazine (9.34g, 70.0mmol), 1-hydroxybenzotriazole hydrate (9.54g, 70.0mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (13.6g, 70.0mmol) in DMF (300mL) was allowed to stir at room temperature for 3h. The mixture was diluted with ethyl acetate (1000mL) and washed with 3N hydrochloric acid (2X), saturated aqueous $NaHCO_3$, water and saturated brine, then were dried ($MgSO_4$), filtered

and concentrated to afford the title compound as a cream solid (26.0g, 94%). ^{1}HNMR (300 MHz, d6-DMSO) d 9.73 (s, 1H), 8.80 (s, 1H), 7.55 (d, 1H), 7.37, s, 5H), 5.03 (s, 2H), 4.13 (m, 1H), 2.53-2.48 (m, 2H), 2.04 (s, 3H), 2.02-1.81 (m, 2H) ,1.40 (s, 9H).

i) N-[benzyloxycarbonylamino-D-methioninyl)-N'-(*tert*-butoxycarbonyl)hydrazide methiodide

A solution of the compound from example 1(h) (26.0, 65.5mmol) in methyl iodide (150mL) was stirred at room temperature for 48h. The mixture was evaporated and the residue co-evaporated with dichloromethane (2X) ro afford the title compound as a pale-yellow solid (33.2g, 95%). MS (ESI): 412 $[M-I]^+$.

(j) (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one

A solution of the compound from example 1(i) (13.0g, 24.2mmol) in DMF (250mL) and dichloromethane (250mL) was cooled to then treated in one portion with sodium hydride (60% *w/w* in mineral oil) (1.94g, 48.4mmol) and the mixture was allowed to stir at 0°C for 3h. Water (20.0mL) was added and the mixture was concentrated then diluted with ethyl acetate (500mL). The solution was washed with 3N hydrochloric acid (2X), saturated aqueous $NaHCO_3$, water and saturated brine, then were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, 50%ethyl acetate/hexane) to yield the title compound as a colorless solid (1.62g, 24%). mp 115-118°C. MS (ESI): 372 $[M+Na]^+$. ^{1}HNMR (300 MHz, d6-DMSO) d 9.31 (s, 1H), 7.73 (d, 1H), 7.37 (s, 5H), 5.06 (s, 2H), 4.16 (m, 1H), 3.42-3.27 (m, 2H), 2.30 (m, 1H), 1.89 (t, 1H), 1.42 (s, 9H).

k) 1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

The compound from example 1(j) (263mg, 0.75mmol) was treated with 4M hydrochloric acid in 1,4-dioxane (2.0mL) and the solution was stirred at room temperature for 1h. The solution was concentrated and the resulting hydrochloride salt was dissolved in DMF (3.0mL), then treated with the compound from example 1(f) (233mg, 0.75mmol), N-methylmorpholine (0.10mL, 0.90mmol), 1-hydroxybenzotriazole hydrate (111mg, 0.82mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (158mg, 0.82mmol). The resulting mixture was stirred at room temperature for 16h then diluted with ethyl acetate (100mL). The solution was washed with 3N hydrochloric acid (2X), saturated aqueous $NaHCO_3$, water and saturated brine, then were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl

acetate/hexane) to yield the title compound as a colorless solid (391mg, 96%). MS (ESI): 543 $[M+H]^+$.

Example 2

Preparation of 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

a) N-benzyloxycarbonyl-L-leucinamide

To a stirring solution of N-benzyloxycarbonyl-L-leucine (4.6 g, 17.3mmol) in THF, cooled to -40 °C, was added N-methylmorpholine (3.68 g, 36.4mmol; 4.0mL) and isobutyl chloroformate (2.37 g, 17.3mmol; 2.25mL). After stirring for 15 min, ammonia was bubbled through the solution for 5 min. The solution was warmed to room temperature, evaporated, and the residue was dissolved in ethyl acetate, washed with 0.1 N HCl, and saturated brine, then dried ($MgSO_4$), filtered and evaporated to dryness to give the title compound as a white solid (4.58 g, 100%).

b) N-benzyloxycarbonyl-L-leucinethioamide

A solution of the compound of Example 1(a) (4.58 g, 17.3mmol) and Lawesson's reagent (4.21 g, 10.4mmol) in THF was allowed to stir at room temperature for 16 h. The solution was concentrated and the residue was purified by flash chromatography on 230-400 mesh silica gel, eluting with 1:3 ethyl acetate/hexanes, to provide the title compound as a pale yellow solid (3.74 g, 77%).

c) (1S)-1-benzyloxycarbonylamino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane

The compound of Example 1(b) (2.20 g, 7.83mmol) was dissolved in acetone (35mL), cooled to -10 °C, and ethyl bromopyruvate (1.68 g, 8.62mmol, 1.08mL) was added. After stirring for 1 h, the solution was poured into dichloromethane/water, then into saturated aqueous $NaHCO_3$. The aqueous layer was extracted dichloromethane and the combined organic layers were washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in dichloromethane, cooled to -20 ° C, pyridine (1.36 g, 17.2mmol, 1.39mL) and trifluroracetic anhydride (1.81 g, 8.62mmol, 1.22mL) were added. After stirring for 1 h, the solution was washed with saturated aqueous $NaHCO_3$ and saturated brine, then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on 90 g of 230-400 mesh silica gel, eluting with 1:3 ethyl acetate/hexanes, to provide the title compound as a pale yellow oil (2.36 g, 80%). ^1H

NMR (400 MHz, $CDCl_3$) d 8.08 (s, 1H), 7.38 (m, 5H), 5.42 (s, 3H), 5.23-5.07 (m, 3H), 4.42 (q, 2H), 2.01-1.62 (m, 3H), 1.41 (t, 3H), 0.99 (d, 6H).

d) 2-[(1S)-1-benzyloxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid

Following the procedure of example 1(f) except substituting (1S)-1-benzyloxycarbonylamino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane for ethyl 2-(2-benzyloxyphenyl)thiazole-4-carboxylate, the title compound was prepared as a colorless solid (900mg, 90%). mp 116-119°C.

e) 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

Following the procedure of example 1(k) except substituting for 2-[1-(S)-benzyloxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid for 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid, the title compound was prepared as a colorless solid (328mg, 77%). ^{1}HNMR (300 MHz, d6-DMSO) d 10.5 (s, 1H), 8.31 (d, 1H), 8.30 (s, 1H), 7.79 (d, 1H), 7.38 (s, 5H), 5.10 (s, 2H), 5.07 (s, 2H), 4.93 (m, 1H), 4.26 (q, 1H), 3.42 (m, 2H), 2.37 (m, 1H), 1.99 (m, 1H), 1.95-1.73 (m, 3H), 0.94 (d, 3H), 0.93 d, 3H).

Example 3

Preparation of 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one

a) (3R)-3-amino-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one

A solution of the compound from example 1(j) (947mg, 2.7mmol) in ethanol (10.0mL) and ethyl acetate (25.0mL) was hydrogenated over 10%w/w palladium on charcoal (95mg, 10%w/w) at atmospheric pressure and room temperature for 16h. The mixture was filtered through a 1" pad of celite then evaporated to afford the title compound as a colorless solid (581mg, 100%). MS (ESI): 216 $[M+H]^+$.

b) 1-(*tert*-butoxycarbonylamino)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one

A solution of the compound from example 3(a) (200mg, 0.93mmol), quinoline-2-carboxylic acid (242mg, 1.4mmol), 1-hydroxybenzotriazole hydrate (188mg, 1.4mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (268mg, 1.4mmol) in DMF (4.0mL) was stirred at room temperature for 16h. The solution was diluted with ethyl acetate (100mL). The solution was washed with saturated aqueous $NaHCO_3$, water and saturated brine, then were dried ($MgSO_4$), filtered and concentrated. The residue was

purified by column chromatography (silica gel, 50% ethyl acetate/hexane) to yield the title compound as a colorless solid (152mg, 48%). ^{1}HNMR (300 MHz, d6-DMSO) d 9.39 (s, 1H), 9.31 (d, 1H), 8.61 (d, 1H), 8.19-8.11 (m, 3H), 7.91 (t, 1H), 7.75 (t, 1H), 4.70 (m, 1H), 3.41-3.35 (m, 2H), 2.51-2.28 (m, 2H), 21.44 (s, 9H).

c) 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one

Following the procedure of example 1(k) except substituting for 2-[1-(S)-benzyloxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid for 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid and 1-(*tert*-butoxycarbonylamino)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid (126mg. 53%). MS (ESI): 601 $[M+H)^+$.

Example 4

Preparation of 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

a) (3S)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one

Following the procedures of example 1(g)-(j) except substituting L-(S)-methionine for D-(R)-methionine the title compound was prepared as colorless solid. MS (ESI): 372 $(M+Na)^+$.

b) (3S)-3-amino-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one

Following the procedure of example 3(a) except substituting (3S)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid (597mg, 100%). MS (ESI): 216 $[M+H]^+$.

c) 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

Following the procedure of example 1(k) except substituting (3S)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one and 2-[1-(S)-benzyloxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid for 2-(2-

benzyloxyphenyl)thiazole-4-carboxylic acid, the title compound was prepared as a colorless solid (304mg, 64%). 602 $[M+Na]^+$, 580 $[M+H]^+$.

Example 5

Preparation of 1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]- (3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one

Following the procedure of example 1(k) except substituting 1-(*tert*-butoxycarbonylamino)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid (146mg, 29%). MS (ESI): 564 $[M+H]^+$.

Example 6

Preparation of 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one

Following the procedure of example 3(a)-(c) except substituting (3S)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a cream solid (103mg, 49%). MS (ESI): 623 $[M+Na]^+$, 601 $[M+H]^+$.

Example 7

Preparation of 1-({2-[(1S)-1-(*tert*-butoxycarbonylamino)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

a) 2-[(1S)-1-*tert*-butoxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid

Following the procedures of example 2(a)-(d) except substituting N-*tert*-butoxycarbonyl-L-leucine for N-benzyloxycarbonyl-L-leucine, the title compound was prepared as a colorless solid. MS (ESI): 313 $[M-H]^-$.

b) 1-({2-[(1S)-1-(*tert*-butoxycarbonylamino)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

Following the procedure of example 1(k) except substituting 2-[(1S)-1-*tert*-butoxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid for 2-(2-

benzyloxyphenyl)thiazole-4-carboxylic acid, the title compound was prepared as a colorless solid (817mg, 99%). MS (ESI): 587 $[M+CH_3CN+H]^+$, 568 $[M+H]^+$, 546 $[M+H]^+$.

Example 8

Preparation of 1-({2-[(1S)-1-amino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one hydrochloride

The compound from example 7(b) (280mg, 0.51mmol) was treated with 4M hydrochloric acid in 1,4-dioxane (2.5mL) and the solution was stirred at room temperature for 0.5h. The solution was concentrated and co-evaporated with toluene (2X) to afford the title compound as a colorless solid (240mg, 97%). ^{1}HNMR (300 MHz, d6-DMSO) d 10.65 (s, 1H), 8.71 (brs, 3H), 8.53 (s, 1H), 7.83 (d, 1H), 7.45-7.33 (m, 5H), 5.07 (s, 2H), 4.82 (m, 1H), 4.26 (m, 1H), 3.57-3.45 (m, 2H), 2.40 (m, 1H), 2.06-1.82 (m, 3H), 1.64-1.55 (m, 1H), 0.94 (d, 3H), 0.92 (d, 3H).

Example 9

Preparation of 1-({2-[(1S)-1-(2-quinolinylcarboxamido)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

Following the procedure of example 1(k) except substituting quinoline-2-carboxylic acid for 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid and 1-({2-[(1S)-1-amino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino) pyrrolidin-2-one hydrochloride for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid, (120mg, 80%). MS (ESI): 601 $[M+H]^+$.

Example 10

Preparation of 1-({2-[(1S)-1-(3-isoquinolinylcarboxamido)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one

Following the procedure of example 1(k) except substituting isoquinoline-3-carboxylic acid for 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid and 1-({2-[(1S)-1-amino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)

pyrrolidin-2-one hydrochloride for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid, (117mg, 78%). MS (ESI): 601 $[M+H]^+$.

Example 11

Preparation of (3S)-3-allyl-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]pyrrolidin-2-one

a) 3-benzyloxycarbonyl-(2S)-2-(*tert*-butyl)-4-[(2R)-2-(methylsulfanyl)ethyl]-1,3-oxazolidin-5-one

A suspension of (R)-D-methionine (14.9g, 100mmol) in ethanol (250mL) was treated with a solution of sodium hydroxide (4.0g, 100mmol) in water (25.0mL) and the mixture was stirred until homogeneous (0.5h). The solution was evaporated and the resulting sodium salt was suspended in hexane (300mL) then treated with trimethylacetaldehyde (12.9g, 150mmol) and the resulting suspension was heated under reflux with azeotropic removal of water (Dean-Stark apparatus) for 24h. The mixture was concentrated and co-evaporated with toluene (2X) to give the corresponding imine as a colorless powder. This powder was suspended in dichloromethane (250mL), cooled to 0°C, then treated with benzyloxycarbonyl chloride (17.1mL, 120mmol) and the resulting suspension was stirred at 0°C for 6d then allowed to warm to room temperature for 24h. The mixture was quenched with water (100mL) and the layers were separated then the aqueous layer was extracted with more dichloromethane (2X). The combined extracts were was washed with 3N hydrochloric acid, saturated aqueous $NaHCO_3$, water and saturated brine, then were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, 5% ethyl acetate/hexane) to yield the title compound as a colorless oil (16.2, 46%). ^{1}HNMR (300 MHz, $CDCl_3$) d 7.38 (s, 5H), 5.57 (s, 1H), 5.18 (s, 2H), 4.53 (t, 1H), 2.78-2.71 (m, 2H), 2.18-2.08 (m, 2H), 2.03 (s, 3H), 0.97 (s, 9H).

b) (2S)-2-benzyloxycarbonylamino-2-[2-(methylsulfanyl)ethyl]-4-pentenoic acid

A solution of the compound from example 11(a) (1.42g, 4.1mmol) in THF (20.0mL) was cooled to -78°C for the dropwise addition of potassium bis(trimethylsilyl)amide (0.5M in toluene) (9.7mL, 5.3mmol) .The yellow anion solution was then immediately treated with allyl bromide (0.35mL, 6.2mmol) and the solution was stirred at -78°C for a further 0.5h. The mixture was quenched by the addition of 10% aqueous potassium hydrogen sulfate (10.0mL) then allowed to warm to room temperature. The solution was then extracted with ethyl acetate and washed with 3N hydrochloric acid,

saturated aqueous $NaHCO_3$, water and saturated brine, then were dried ($MgSO_4$), filtered and concentrated. The crude product (which showed the presence of only a single diastereomer by 1HNMR) was dissolved in methanol (20.0mL) and 10% aqueous sodium hydroxide (20.0mL) then heated under reflux for 24h. The solution was then concentrated, treated with 3N hydrochloric acid and extracted with ethyl acetate. The extracts were washed with and saturated brine, then were dried ($MgSO_4$), filtered and concentrated to afford the title compound as a yellow oil (1.17g, 88%). MS(ESI): 322 $[M-H]^-$.

c) N-{(2S)-2-benzyloxycarbonylamino-2-[2-(methylsulfanyl)ethyl]-4-pentenoyl}-N'-(*tert*-butoxycarbonyl)hydrazide

Following the procedure or example 1(h) except substituting (2S)-2-benzyloxycarbonylamino-2-[2-(methylsulfanyl)ethyl]-4-pentenoic acid for benzyloxycarbonyl-D-methionine, the title compound was prepared as a colorless solid. (1.26g, 86%). MS(ESI): 460 $[M+Na]^+$.

d) N-{(2S)-2-benzyloxycarbonylamino-2-[2-(methylsulfanyl)ethyl]-4-pentenoyl}-N'-(*tert*-butoxycarbonyl)hydrazide methiodide

Following the procedure or example 1(i) except substituting N-{(2S)-2-benzyloxycarbonylamino-2-[2-(methylsulfanyl)ethyl]-4-pentenoyl}-N'-(*tert*-butoxycarbonyl)hydrazide for N-[benzyloxycarbonylamino-D-methioninyl)-N'-(*tert*-butoxycarbonyl)hydrazide, the title compound was prepared as a yellow solid (1.61g, 96%). MS(ESI): 452 $[M-I]^+$.

e) (3S)-3-allyl-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]pyrrolidin-2-one

Following the procedure for example 1(j) except substituting N-{(2S)-2-benzyloxycarbonylamino-2-[2-(methylsulfanyl)ethyl]-4-pentenoyl}-N'-(*tert*-butoxycarbonyl)hydrazide methiodide for N-[benzyloxycarbonylamino-D-methioninyl)-N'-(*tert*-butoxycarbonyl)hydrazide methiodide, the title compound was prepared as a colorless solid (364mgg, 35%). ^{1}HNMR (300 MHz, d6-DMSO) d 9.37 (brs, 1H), 7.54 (brs, 1H), 7.36 (s, 5H), 5.90 (m, 1H), 5.22-5.13 (m, 2H), 5.00 (s, 2H), 3.37-3.33 (m, 2H), 2.35-2.32 (m, 3H), 2.01 (m, 1H), .1.41 (s, 9H).

f) 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-allyl-3-(benzyloxycarbonylamino)pyrrolidin-2-one

Following the procedure for example 1(k) except substituting (3S)-3-allyl-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one for (3R)-3-

benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid (103mg, 67%). ^{1}HNMR (300 MHz, d6-DMSO) d 10.93 (s, 1H), 8.64 (d, 1H), 8.41 (s, 1H), 7.60 7.32 (m, 14H), 7.16 (t, 1H), 6.06 (m, 1H), 5.43 (s, 2H), 5.26-5.16 (m, 2H), 5.03 (s, 2H), 3.54-3.40 (m, 3H), 2.48-2.37 (m, 2H),

Example 12

Preparation of (3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(cyclopropylmethyl)pyrrolidin-2-one

a) (3R)-3-(benzyloxycarbonylamino)-1-(tert-butoxycarbonylamino)-3-(cyclopropylmethyl)pyrrolidin-2-one

The compound from example 11(e) (115mg, 0.32mmol) was treated with ethereal diazomethane (0.4M) (5.0ml, 1.9mmol) then cooled to 0°C for the addition of palladium acetate (ca. 10mg), then stirred at 0°C for a further 10min. The mixture was diluted with diethyl ether then filtered through a pad of celite. The filtrate was concentrated to afford the title compound as a tan solid (124mg, 96%). ^{1}HNMR (300 MHz, d6-DMSO) d 9.34 (brs, 1H), 7.42-7.31 (m, 6H), 5.00 (s, 2H), 3.45-3.40 (m, 2H), 2.41 (m, 1H), 2.27 (m, 1H), 1.55-1.30 (m, 2H), 1.40 (s, 9H), 0.89 (m, 1H), 0.46-0.43 (m, 2H), 0.15-0.06 (m, 2H).

b) 3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-(3S)-3-(cyclopropylmethyl)pyrrolidin-2-one

Following the procedure for example 1(k) except substituting) (3R)-3-(benzyloxycarbonylamino)-1-(*tert*-butoxycarbonylamino)-3-(cyclopropylmethyl) pyrrolidin-2-one for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid (66.7mg, 53%). MS (ESI): 619 $[M+Na]^+$, 597 $[M+H]^+$.

Example 13

Preparation of (3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-propylpyrrolidin-2-one

a) (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)-3-propylpyrrolidin-2-one

A solution of the compound from example 11(e) (118mg, 0.30mmol) in ethanol (5.0mL) was hydrogenated over 10%w/w palladium on charcoal (ca. 10mg) at room temperature and atmospheric pressure for 16h. The mixture was filtered through celite and

concentrated to afford the title compound as a colorless solid (94mg, 80%). MS(ESI): 392 [M+H]+.

b) (3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-propylpyrrolidin-2-one

Following the procedure for example 1(k) except substituting (3S)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)-3-propylpyrrolidin-2-one for (3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one, the title compound was prepared as a colorless solid (64.4mg, 48%). MS (ESI): 607 $[M+Na]^+$.

Example 14

Preparation of (3S)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(2-methylallyl)pyrrolidin-2-one

Following the procedures of example 11(a)-(e) except substituting 2-methylallylbromide for allyl bromide in example 11(b), the title compound was prepared as a colorless solid (92.9mg, 46%). MS(ESI): 619 $[M+Na]^+$, 597 $[M+H]^+$.

Example 15

Preparation of (3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(2-methylpropyl)pyrrolidin-2-one

Following the procedures detailed previously, the title compound was prepared.

Example 16

Preparation of (3R)-3-(2-methylpropyl)-1-[2-(1-napthyl)phenylthiazol-4-ylcarboxamido]-3-(8-quinolinecarboxamido)pyrrolidin-2-one

Following the procedures detailed previously, the title compound was prepared.

Example 17

Preparation of 1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-methylpropyl)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one

Following the procedures detailed previously, the title compound was prepared.

Example 18

Preparation of 1-[2-(1-napthyl)phenylthiazol-4-ylcarboxamido]-(3R)-3-(8-quinoline-carboxamido)pyrrolidin-2-one

Following the procedures detailed previously, the title compound was prepared.

Example 19

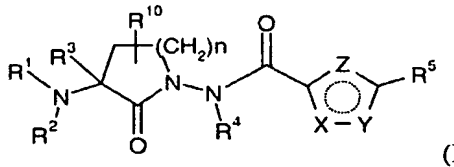
Preparation of 3-benzyloxycarbonylamino-1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-methylpropyl)pyrrolidin-2-one

Following the procedures detailed previously, the title compound was prepared.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I):



(I)

wherein:

X, Y and Z independently are N, O, S or CR', provided that at least two of X, Y and Z are heteroatoms and at least one of X, Y and Z is N; or one of X, Y and Z is C=N, C=C or N=N and the other two are CR' or N, provided that X, Y and Z together comprise at least two N;

--- indicates a single or double bond;

R^1 is R", R"C(O), R"C(S), R"SO_2, R"OC(O), or R"OC(O)NR'CH(R^6)C(O);

R^2 is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^3 is H, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^4 is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^5 is C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, CH(R^6)NR'R^7, CH(R^6)Ar, CH(R^6)OAr, or NR^8R^9;

each R^6 independently is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl;

R^7 is R", R"C(O), R"C(S), R"SO_2, R"OC(O), or R"OC(O)NR'CH(R^6)C(O);

R^8 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl and R^9 is C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; or R^8 and R^9 are combined to form a 3-7 membered monocyclic or 7-10-membered bicyclic carbocyclic or heterocyclic ring, optionally substituted with 1-4 of C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkoxy, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}$NR'R", or O$(CH_2)_{1-6}$NR'R";

R^{10} is H, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

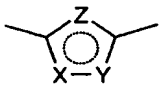
each R' independently is H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

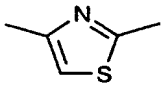
each R" independently is C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; and

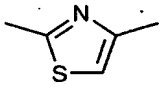
n is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein



is


or


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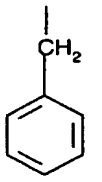
3. A compound according to claim 1 wherein R^2, R^4 and R^{10} are H and R^3 is H, C_{1-6}alkyl, C_{2-6} alkenyl or C_{3-6}cycloalkyl-CH_2.

4. A compound according to claim 1 wherein R^5 is $CH(R^6)NR'R^7$, in which R^6 in said R^5 group is i-butyl and R' in said R^5 group is H.

5. A compound according to claim 4 wherein R^7 is $R''OC(O)$ or $R''C(O)$, in which R'' in said R^7 group is C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl,

6. A compound according to claim 5 wherein R'' in said R^7 group is



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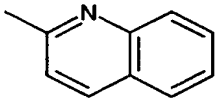
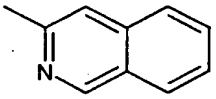


or


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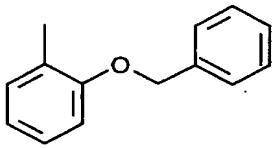
7. A compound according to claim 1 wherein R^5 is Ar, in which Ar in said R^5 group is



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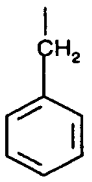
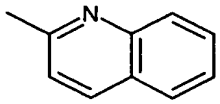
8. A compound according to claim 1 wherein R^1 is $R''OC(O)$ or $R''C(O)$, in which R'' in said R^1 group is



or



9. A compound according to claim 1 wherein n is 1 or 2.

10. A compound according to claim 9 wherein n is 1.

11. A compound according to claim 1 which is:
1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3S)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-({2-[(1S)-1-(tert-butoxycarbonylamino)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-amino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-(2-quinolinylcarboxamido)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
1-({2-[(1S)-1-(3-isoquinolinylcarboxamido)-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(benzyloxycarbonylamino)pyrrolidin-2-one;
(3S)-3-allyl-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]pyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(cyclopropylmethyl)pyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-propylpyrrolidin-2-one;

(3S)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(2-methylallyl)pyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-[2-(2-benzyloxy)phenylthiazol-4-ylcarboxamido]-3-(2-methylpropyl)pyrrolidin-2-one;
(3R)-3-(2-methylpropyl)-1-[2-(1-napthyl)phenylthiazol-4-ylcarboxamido]-3-(8-quinolinecarboxamido)pyrrolidin-2-one;
1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-methylpropyl)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-[2-(1-napthyl)phenylthiazol-4-ylcarboxamido]-(3R)-3-(8-quinolinecarboxamido)pyrrolidin-2-one; or
3-benzyloxycarbonylamino-1-({2-[(1S)-1-benzyloxycarbonylamino-3-methylbutyl]thiazol-4-yl}carboxamido)-(3R)-3-(2-methylpropyl)pyrrolidin-2-one;
or pharmaceutically acceptable salts thereof.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A method of inhibiting a cysteine protease which comprises administering a compound according to claim 1.

14. A method according to claim 13 wherein the cysteine protease is cathepsin K.

15. A method of inhibiting bone loss which comprises administering a compound according to claim 1.

16. A method of treating osteoporosis which comprises administering a compound according to claim 1.

17. A method of treating gingival or peridontal disease which comprises administering a compound according to claim 1.

18. A method of treating a disease characterized by excessive cartilage or matrix degradation which comprises administering a compound according to claim 1.

19. A method according to claim 18 wherein said disease is osteoarthritis or rheumatoid arthritis.

20. A compound which is:
2-benzyloxyphenylboronic acid;
ethyl 2-(2-benzyloxyphenyl)thiazol-4-carboxylate;
2-(2-benzyloxyphenyl)thiazol-4-carboxylic acid;
(3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one;
(3S)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one;
1-(*tert*-butoxycarbonylamino)-(3R)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
1-(*tert*-butoxycarbonylamino)-(3S)-3-(2-quinolinylcarboxamido)pyrrolidin-2-one;
(1S)-1-benzyloxycarbonylamino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane;
2-[(1S)-1-benzyloxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid;
(1S)-1-tert-butoxycarbonylamino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane;
2-[(1S)-1-*tert*-butoxycarbonyl)-3-methylbutyl]thiazole-4-carboxylic acid;
(3S)-3-allyl-3-(benzyloxycarbonylamino)-1-(*tert*-butoxycarbonylamino)pyrrolidin-2-one;
(3R)-3-benzyloxycarbonyl-1-(*tert*-butoxycarbonylamino)-3-propylpyrrolidin-2-one;
(3R)-3-(benzyloxycarbonylamino)-1-(*tert*-butoxycarbonylamino)-3-(cyclopropylmethyl)pyrrolidin-2-one; or
(3S)-3-(benzyloxycarbonylamino)-1-(*tert*-butoxycarbonylamino)-3-(2-methylallyl)pyrrolidin-2-one.

21. A compound according to any one of claims 1 to 11 for use as a medicament.

22. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which inhibition of a cysteine protease is a factor.

23. The use of a compound according to claim 22 wherein the cysteine protease is cathepsin K.

24. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of bone loss.

25. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of osteoporosis.

26. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of gingival or peridontal disease.

27. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases characterized by excessive cartilage or matrix degradation.

28. The use of a compound according to claim 27 wherein the disease characterized by excessive cartilage or matrix degradation is osteoarthritis or rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07969

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 277/04
US CL :548/184, 185, 188; 514/385

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/184, 185, 188; 514/385

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

IS&R, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,937,335 A (ISHIMITSU et al) 26 June 1990, columns 1 and 2.	1-28
A	US 5,244,867 A (DITRICH et al) 14 September 1993, columns 1-4.	1-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

10 JUNE 1998

Date of mailing of the international search report

04 SEP 1998

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet)(July 1992)☆

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07969

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-28

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07969

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

Group I: Claim(s) 1 - 28, drawn to compounds, compositions, methods and uses wherein Z is C=N; either X or Y is CR', and the other is S.
Group II: Claim(s) 1, 3 - 28 (part of each), drawn to compounds, compositions, methods and uses wherein Z is C=N; either X or Y is O, and the other is S.
Group III: Claim(s) 1, 3 - 28 (part of each), drawn to compounds, compositions, methods and uses wherein Z is C=C; either X or Y is N, and the other is S.
Group IV: Claim(s) 1, 3 - 28 (part of each), drawn to compounds, compositions, methods and uses wherein Z is N=N; either X or Y is O, and the other is S.
Group V: Claim(s) 1, 3 - 28 (part of each), drawn to compounds, compositions, methods and uses wherein Z is C=N; either X or Y is CR', and the other is O.
Group VI: Claim(s) 1, 3 - 28 (part of each), drawn to compounds, compositions, methods and uses wherein Z is C=C; either X or Y is N, and the other is O.
Group VII: Claim(s) 1, 3 - 28 (part of each), drawn to compounds, compositions, methods and uses wherein Z is N=N; either X or Y is CR', and the other is S.
Group VIII: Claim(s) 1, 3 - 28 (part of each) drawn to compounds, compositions, methods and uses wherein Z is N=N; either X or Y is CR', and the other is O.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

1. The ring with heteroatoms represented by X, Y and Z is considered as the "special technical feature".

2. As X, Y and Z vary, the "special technical feature" differs from one group to the next.